26. (Amended) An antisense nucleic acid against TRELL comprising a nucleic acid sequence hybridizing under stringent hybridization ~~conditions~~ to at least a portion of SEQ[.] ID[.] NO[.]:1 ~~or~~ SEQ[.] ID[.] NO[.]:3 effective to inhibit expression of ~~TRELL~~.

REMARKS

Reconsideration and allowance are requested.

Claims 1-35 are pending in this application. Claims 11-25, 27 and 32-35 are withdrawn from consideration by the Examiner.

In the present Amendment, claims 1-5, 7, 9 and 10 are amended. Claims 1-5 and 9 are amended to recite "substantially purified" DNA sequences. This amendment is supported throughout the Specification, for example, at page 11, lines 2-3. Claim 1 is amended to recite DNA sequences "comprising (a) SEQ ID NO:1 or an equivalent thereof; or (b) SEQ ID NO:3 or an equivalent thereof." This amendment is supported throughout the Specification, for example, at page 11, lines 2-10. Claims 2-5, 7 and 9 have been amended to correct informalities in the "SEQ ID NO:". Claim 4 is amended to recite "the receptor binding domain of TRELL." This Amendment is supported, for example, at page 11, lines 16-18. Claim 5 is amended to recite "substitutions, alterations or deleting which do not abolish the biological activity of TRELL." This amendment is supported, for example, at page 18, line 26. Claim 10 has been amended to recite the step of "substantially purifying TRELL from said transformed host." This amendment finds support throughout the Specification, for example, at page 7, lines 28-30; page 9, line 32 to page 10, line 2 and at page 34, line 24 to page 35, line 9. Claim 26 is amended to recite an antisense nucleic acid "effective to inhibit expression of TRELL." This amendment is supported, for example, at page 13, lines 25-28, of the Specification. No new matter has been added. Accordingly, claims 1-10, 26 and 28-31 are at issue in this case.

The Specification has been amended to include specific reference to the earlier-filed applications to which the present application claims priority under 35 U.S.C. 119(e).

The Examiner has objected to the abstract of the disclosure because the sentence is incomplete. By the present Amendment, Applicants have amended the Abstract to a complete sentence, and accordingly request withdrawal of this rejection.

The Examiner has also objected to several informalities in the Specification. By the present amendment, Applicants have corrected these informalities in the Specification. No new matter has been added. Accordingly, Applicants request withdrawal of these objections.

Claim 5 is objected to under 37 CFR 1.75(c) as being of improper dependent form. As suggested by the Examiner, claim 5 has been rewritten in independent form. Accordingly, Applicants request withdrawal of this objection.

Claims 2-5, 7, 9 and 26 are objected to because of informalities. By the present amendment, Applicants have amended the claims to remove the multiple periods in the claims and to recite "SEQ ID NO:". Accordingly, Applicants believe that the claims are in proper form and respectfully request withdrawal of the objections.

Claims 1-10, 26 and 28-31 stand rejected under 35 U.S.C. 101. The Examiner asserts that the claimed invention is not supported by either a specific and substantial utility or a well-established utility. Applicants respectfully traverse this rejection.

The present claimed invention is directed to nucleic acids that encode a TNF-family protein designated "TRELL". One page 6 of the Office Action, the Examiner identifies a number of utilities for the claimed invention that are disclosed in the Specification. However, Applicants note that the application "need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112." (MPEP §2107.01(I); page 2100-29 Rev. 1, Feb. 2000). Applicants submit that the present Specification provides at least one specific, substantial and credible utility for the claimed invention.

As described in the Patent Office Guidelines For Examination of Applications for Compliance With The Utility Requirement of 35 U.S.C. 101 and 35 U.S.C. 112 (MPEP §706.03(a)(i)), determination of utility is based on an analysis that involves (1.) review of application to identify an assertion that the claimed invention is useful for a particular purpose (a "specific and substantial utility"), and (2.) assessment of whether the utility is credible from the standpoint of one of ordinary skill in the art.

As described throughout the Specification (and noted by the Examiner on page 6 of the Office Action), "the claimed invention is involved in the induction of cell death in carcinoma." (page 7, lines 1-2). Applicants submit that they have clearly made a *specific* assertion of utility, linked to the particular nucleic acids and proteins as claimed. This specific utility identified by Applicants is a *substantial* utility in that it defines a "real world" use; i.e., induction of cell death in carcinoma, which has obvious therapeutic and pharmacological benefits.

Applicants respectfully remind the Examiner that, as set forth in MPEP §2107(I):

> Office personnel also must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., *Brenner v. Manson,* 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "specific" utility.

Accordingly, Applicants submit that they have appropriately identified a specific and substantial utility.

Furthermore, this utility identified by Applicants is *credible* in light of the state of the art and the disclosure provided by Applicants in the application. As demonstrated by the experimental evidence and results provided in Table II (page 37) of the application, Applicants have shown that TRELL binds to colon adenocarcinoma cells and has cytotoxic effects on such cells.

Without addressing whether this utility is a well-established utility recognized by those skilled in the art, Applicants submit that the evidence provided in the application is more than sufficient to establish the credibility of the asserted utility. As stated in MPEP §2107.02(III), "data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Accordingly, Applicants submit that the present application provides a specific, substantial and credible utility for the claimed invention sufficient to meet the requirements of 35 U.S.C. 101, and accordingly Applicants request withdrawal of this rejection.

Claims 1-10, 26 and 28-31 stand rejected under 35 U.S.C. 112, first paragraph. The Examiner asserts that since the claimed invention is not supported by either a specific and substantial utility or a well-established utility, one skilled in the art would not know how to use the claimed invention. This rejection is respectfully traversed for the reasons detailed below.

As discussed above, the present application provides support for a specific, substantial and credible utility for the claimed invention, and the same reasoning and arguments detailed above apply here as well.

Furthermore, Applicants submit that the application contains sufficient disclosure to enable one of ordinary skill in the art to make and use the claimed invention. Pages 11-14 of the Specification describe the nucleic acids and equivalents claimed in the present invention, as well as production of expression vectors containing the nucleic acid sequences, and transformation of appropriate hosts to produce TRELL. Pages 13-14 also describe use of the nucleic acids of the invention in gene therapy and antisense therapy. The application provides reference to exemplary nucleic acid molecules for use as antisense oligonucleotides (page 14, lines 5-7) and to approaches to constructing oligomers useful in antisense therapy (page 14, lines 7-10; the references incorporated into the application are attached at Exhibit A hereto, for the convenience of the Examiner).

Applicants submit that the disclosure in the present application and the incorporated references, in light of the understanding of one skilled in the art, provide sufficient guidance to one of ordinary skill in the art to enable him or her to make and use the claimed polynucleotides and peptides without undue experimentation. Applicants therefore request withdrawal of this rejection.

Claims 1, 4-10, 26 and 28-31 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. The Examiner contends that there is no disclosure in the Specification of genomic sequences that comprise the nucleic acids associated with the claimed polynucleotides. Applicants respectfully traverse this rejection.

The present application discloses full open reading frames ("ORFs") from mouse (SEQ ID NO:1) and human (SEQ ID NO:3) nucleic acid sequences that encode TRELL polypeptide.

Applicants submit that one of ordinary skill in the art can readily envisage nucleic acid sequences which include SEQ ID NO: 1 or SEQ ID NO:3 because these sequences can be readily embedded in known vectors, as understood in the art and as taught by Applicants in the Specification at, e.g., page 12, line 3 to page 13, line 10. Although there may be substantial variability among the DNA species encompassed within the scope of the claims, because SEQ ID NOs 1 and/or 3 may be combined with sequences known in the art, the necessary common attribute is the ORF of SEQ ID NOs 1 or 3. Taking Applicants disclosure in view of the level of knowledge and skill in the art, one skilled in the art would recognize from the disclosure that Applicants were in possession of the genus of DNAs that comprise SEQ ID NOs 1 and 3, as claimed in the present application. Accordingly, Applicants request withdrawal of this rejection.

Claims 1-10, 26 and 28-31 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection, and request reconsideration and withdrawal.

The Examiner asserts that claim 1 is vague and indefinite because it is unclear which sequence encoding TRELL and which fragment thereof is intended.

Applicants have amended claim 1 to delete claim language relating to "fragments thereof" and to specify that the claimed DNA sequences comprise "(a) SEQ ID NO:1, or an equivalent thereof; or (b) SEQ ID NO:3 or an equivalent thereof." Accordingly, Applicants submit that claim 1 sets forth the metes and bounds of the DNA sequences encoding TRELL and Applicants request withdrawal of this rejection.

The Examiner contends that claim 4 is rendered vague and indefinite by the phrase "an active site of TRELL" and it is unclear what hybridization conditions are necessary.

By the present amendment, Applicants have deleted claim language reciting "an active site of TRELL", thereby obviating this rejection. With respect to the hybridization conditions, applicants have amended claims 4 and 28 to specifically refer to "stringent" hybridization conditions. Stringent hybridization conditions have been well documented and are well-known in the art.*[1] As such, applicants submit that the skilled artisans would readily appreciate the

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[1] See, for example, Maniatis et al., "Molecular Cloning: A Laboratory Manual," Cold Spring Harbor Press (1982), T.I. Bonner et al., "Reduction In The Rate of DNA Reàssociation By Sequence Divergence" J.Mol.Biol., 81, p. 123 (1973) and C. Schildkraut et al., Biopolymers 3, p. 195 (1965). For the convenience of the Examiner, a copy of the Bonner and Schildkraut papers are included herewith at Exhibit B.

meaning of the term "stringent" hybridization conditions and would be able to determine the metes and bounds of a patent claim using that terminology.

Accordingly, withdrawal of this rejection is requested.

The Examiner also contends that claim 5 is vague and indefinite in its use of the term "A" and the phrase "said sequence consists essentially of SEQ ID NO 1 or SEQ ID NO 3 with conservative substitutions, alterations or deletions." This rejection is respectfully traversed.

As suggested by the Examiner, Applicants have amended claim 5 to be an independent claim, have replaced "consisting essentially of" with "comprises," and have amended the claim to recite "conservative substitutions, alterations or deletions which do not abolish the biological activity of TRELL". Applicants submit that claim 5 meets the requirements of 35 U.S.C. 112. Accordingly, withdrawal of this rejection is requested.

The Examiner further contends that claim 10 is rendered vague and indefinite by the phrase "producing substantially pure TRELL," and the phrase "unicellular host". This rejection is respectfully traversed.

Claim 10 has been amended to delete the term "unicellular" and to include a step of "substantially purifying TRELL from said transformed host." Furthermore, Applicants note that at page 9, line 32 to page 10, line 2 of the Specification, a definition of "substantially pure" is provided. Accordingly, Applicants submit that claim 10 is sufficiently clear and definite to meet the requirements of 35 U.S.C. 112, second paragraph.

The Examiner also asserts that claim 26 is rendered vague and indefinite by the phrase "at least a portion." This rejection is respectfully traversed.

Applicants submit that the phrase "at least a portion of", as used in claim 26, is sufficiently clear and definite to permit one of ordinary skill in the art to practice the claimed invention. In the context of claim 26 and the present application, one of ordinary skill in the art will appreciate that claim 26 is directed to nucleic acid sequences that will hybridize (under stringent conditions) to complementary sequences in SEQ ID NO:1 or SEQ ID NO:3. The phrase "at least a portion" will be understood by its generally-accepted meaning, i.e., "a part or limited quantity of anything" (Webster's New World Dictionary, Third College Edition, 1988, MacMillan - see Exhibit C), such that one of ordinary skill in the art will appreciate that the claimed antisense nucleic acids hybridize to at least some part or limited quantity of the

designated sequences, and not necessarily to the *entire* sequence. Accordingly, Applicants request withdrawal of this rejection.

Claims 1, 4, 5 and 26 stand rejected under 35 U.S.C. 102(b) as anticipated by Matsubara et al. (WO 95/14772). The Examiner asserts that Matsubara et al. teach a 264 base pair nucleotide sequence which has 97.3% best local similarity to base pairs 1111 to 1373 of SEQ ID NO:3 of the present application. The Examiner contends that the Matsubara et al. sequence is a fragment of TRELL, consists of at least 20 consecutive bases of SEQ ID NO:3, is likely to hybridize to SEQ ID NO:3 and necessarily comprises the complementary strand of SEQ ID NO:3. This rejection is traversed for the reasons detailed below.

As set forth in Scripps Clinic Research Foundation v. Genentech, Inc., 18 U.S.P.Q. 2d 2001, 1010 (Fed. Cir.1991): "anticipation requires that all of the elements and limitations of the claims are found within a single prior art reference. (citations omitted). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." For the following reasons, Matsubara et al. fail to disclose the elements and limitations of the present claims.

Claim 1 of the present invention is directed to a DNA sequence encoding TRELL. Matsubara et al. merely disclose an EST and the sequence does not encode a protein, and in particular does not encode TRELL.

Claim 4 is directed to DNA sequences that hybridize under stringent conditions to a sequence encoding a polypeptide homologous to the receptor binding domain of TRELL. Matsubara et al. merely disclose an EST and they do not disclose homology with specific domains of any polypeptide, particularly not the receptor binding domain of TRELL.

Claim 5 is directed to DNA sequences with conservative substitutions, alterations or deletions which do not abolish the biological activity of TRELL. Matsubara et al. merely disclose an EST and do not disclose or suggest that the sequence encodes a biologically active polypeptide, particularly biologically-active TRELL.

Claim 26 is directed to an antisense nucleic acid hybridizing under stringent conditions to at least a portion of SEQ ID NOS:1 or 3 effective to inhibit expression of TRELL. Matsubara et al. merely disclose an EST and do not disclose or suggest inhibition of expression of TRELL.

Accordingly, Applicants submit that the present invention is not anticipated by Matsubara et al., and respectfully request withdrawal of this rejection.

The Examiner also asserts that the application fails to comply with the requirements of 37 C.F.R. 1.821(d). She contends that reference must be made to the sequences disclosed on pages 27-29, 32 and 33 in the text by use of the sequence identifier and further, that Figures 1 and 2 contain sequences which have no sequence identifiers.

By the present amendment, the Specification has been amended to include "SEQ ID NO" designations where appropriate. In addition, Applicants submit herewith a revised Sequence Listing (in computer-readable form and paper copy) that includes the sequences identified in the text of the Specification and in the Figures. Accordingly, Applicants submit that the present application is in compliance with 37 C.F.R. 1.821 and they respectfully request withdrawal of this objection.

CONCLUSION

Applicants submit that, in light of the above amendments and remarks, the present application is in condition for allowance and such action is respectfully requested. If the Examiner believes that it would help expedite prosecution of this application, she is invited to contact the undersigned attorney at (617) 679-3795 to discuss any outstanding issues of patentability.

Respectfully submitted,

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